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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,921	09/24/2001	Didier Raoult		3015

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EXAMINER	
BASKAR, PADMAVATHI	
ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,921	RAOULT ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,10,11,15,25 and 29-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,10, 11, 15, 25, 29 and 30-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Upon further review of the application, the allowance has been withdrawn and the same is informed to the applicant dated on 7/21/06 (See 37 CFR 1.313(b)(3)).

Prosecution on the merits of this application is reopened on claims 1, 10, 11, 15, 25 , 29, 30, 31 and 32 considered unpatentable for the reasons indicated below in the action and especially claim 1 because applicant is not claiming the same *Tropheryma whippelii* culture as deposited under CNCM of the Institute Pasteur under Deposit No. 1-2202 and therefore, the art of record applies to the claims as set forth below in the Office action.

Status of claims

2. Claims 1,10, 11, 15, 25, 29 and 30-32 are pending and are under examination in the application.

New Claim Rejections - 35 USC 112, first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

4 Claims 1, 10, 11, 15, 25 , 29, 30, 31and 32 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claim 1 is drawn a culture comprising a bacterium responsible for Whipple's disease, said bacterium being isolated and established in culture such that the bacterium reproducibly multiplies over time, wherein the bacterium is of the same species as the *Tropheryma whippelii* bacterium strain deposited in the CNCM of the Institute Pasteur under Deposit No. 1-2202, Claim 10 is drawn to an antigen isolated from a *Tropheryma whippelii* bacterium, wherein said

antigen is a protein of 200 kD determined by polyacrylamide gel electrophoresis using the Western blotting technique, which reacted with specific monoclonal antibody directed against the bacterium *Tropheryma whippelii* responsible for Whipple's disease or an antigen of said bacterium, said antibody being produced by a hybridoma deposited in the CNCM of the Institute Pasteur under the Deposit No. 1-2411. Claims 11 and 15 are drawn to a method for the in vitro diagnosis of diseases associated with infections caused by *Tropheryma whippelii,* comprising contacting serum or any other biological fluid of a patient with a culture according to claim 1 or a *Tropheryma whippelii* bacterium obtained from said culture, and detecting an immunological reaction , said method comprising depositing a solution containing said *Tropheryma whippelii* bacterium in or on a solid support; introducing serum or any other biological fluid into or onto said support, introducing a solution of a labeled antibody specific for a human immunoglobulin, which recognizes said bacterium and detecting an immunological reaction. Claims 25 and 29 are drawn to a method for the in vitro diagnosis of diseases associated with infections caused by *Tropheryma whippelii,* comprising contacting serum or any other biological fluid of a patient with an antigen according to claim 10 and detecting an immunological reaction , said method comprising depositing a solution containing said *Tropheryma whippelii* bacterium in or on a solid support; introducing serum or any other biological fluid into or onto said support, introducing a solution of a labeled antibody specific for a human immunoglobulin, which recognizes said bacterium and detecting an immunological reaction, wherein said culture is not a cell culture in monocyte cells (claim 30), a cell culture in immortalized cells (claim 31) , said immortalized cells are fibroblast cells (claim 32).

The specification teaches that the novel TWIST-Marseille strain Tropheryma whippelii was cultivated on embryonic human fibroblasts continuously and deposited in the CNCM under deposit no 1-2202. However, it appears that more than one strain of bacteria

and heterogeneity exists among whipple's disease associated bacteria . Therefore, it is expected that different strains would have different sequences and different proteins as known in the art of bacteriology. Given that only TWIST-Marseille strain Tropheryma whippelii is cultured, given that there are different strains exists, the structure and function of other unknown/uncharacterized stains as claimed do not have written description support .

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id. The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002).

The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the strain *Twist-Marseille Tropheryma whippelii CNCM 1-2202*, per Lilly by structurally describing a representative number of strains /species of *Tropheryma whippelii* that these species, responsible for Whipple's disease have been continuously cultured or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is

complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe claimed bacteria that are isolated and established in culture which are responsible for whipple's disease which are of the same species as *Tropheryma whippelii Twist-Marseille CNCM 1-2202 or antigen produced from various species of Tropheryma whippelii* required to practice the claims 1 10, 11, 15, 25 , 29, 30, 31, 32 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any other species/strains *Tropheryma whippelii* nor does the specification provide any partial structure of such species/strains , nor any physical or chemical characteristics of the *Tropheryma whippelii* nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a *Tropheryma whippelii species CNCM*, this does not provide a description of other species/strains of *Tropheryma whippelii* , that are responsible for whipple's disease, which claimed bacterium or antigen responsible for whipple's disease in culture, capable of diagnosing Whipple's disease associated diseases that would satisfy the standard set out in Enzo.

The specification also fails to disclose claimed bacteria that are isolated and established in culture which are responsible for whipple's disease which are of the same species as *Tropheryma whippelii Twist-Marseille CNCM 1-2202* by the test set out in Lilly. The specification describes only a single *Tropheryma whippelii species CNCM and an antigen isolated therefrom.* Therefore, it necessarily fails to describe a "representative number" of such species/strains *Tropheryma whippelii* and antigens. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the *Tropheryma whippelii* species/strains or antigen that is required to practice the claimed invention. Since the specification fails to adequately describe the strains and antigen that are capable of functioning as claimed it also fails to adequately describe the claimed methods .

Claims 1, 10, 11, 15, 25 , 29, 30, 31and 32 are also rejected under 35 U.S.C. 112 first paragraph for lack of enablement as specification fails to disclose the broadly claimed invention.

Claim Rejections - 35 USC 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Schoedon et al 1997

Schoedon et al disclose a culture comprising isolation of *Tropheryma whippelii* bacterium (see Journal Infectious diseases, 176; 672-677) responsible for Whipple's disease (see abstract) from biopsy material obtained from a patient. The bacterium is cultured in medium containing (see figure1) deactivated mononuclear phagocytes (see page 673, right column, under inoculation of cultures) and this bacteria has been expanded in a large volume of cells SigM5 in growth medium (see page 673, right column) thus appears to be the same species as deposited under CNCM of the Institute Pasteur under Deposit No1-2202 an thus read on claim 1. Since isolated bacteria is routinely used as an antigen in the art, the bacteria isolated from PMNC read on claim 10 because these claims do not distinguish the bacterium from the prior art as the art disclosed the same *Tropheryma whippelii.* The prior art anticipated the claimed invention.

8. Claims 1, 30 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Muller et al 1999 GASTROENTEROLOGY. Vol, 116, No. 4. Part 2, Abstract 910, 1999. (Abstract only)

The prior art discloses *T.whippelii* replicate in IL4 treated monocytic U937 cell line (see abstract) and thus the bacteria multiply over the time as in the claimed invention. Since isolated bacteria is cultured , these claims do not distinguish the bacterium from the prior art as the art disclosed the same *species Tropheryma whippelii.* The prior art anticipated the claimed invention.

9. Claims 1, 30 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Drancourt 1999 Presse Medicale, Vol. 2: No. 8, February 27. 1 999, pp. 435-439 (See translated article) .

The prior art discloses *T.whippelii* is isolated from two heart valves sampled from two patients, deactivated by a combination of dexamethasone, interleukin-4 (1L-4) and IL10 (see Table 1) and bacteria was cultivated or propagated in human cell line, monoblast SigM5 (see page 8, bottom of the page) and thus the bacteria multiply over the time. This cell line grows continuously in cell culture as SigM5 is an immortalized cell line and it is not primary human monocytes and thus meets the limitations of claim 30 and 31. Since , the bacteria isolated and propagated in the culture it read on claims because these claims do not distinguish the bacterium from the prior art as the art disclosed the same *Tropheryma whippelii.* The prior art anticipated the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 11, 15, 25 and 29 –32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller or Schoedon or Drancourt in view of Kent (abstract only, ARCH.PATHOL.LAB.MED 1980, 104 (10) 544-547 and Harlow and Lane 1986, Cold Spring Harbor Laboratory 1988, (chapters 14/5/6) .

Muller or Schoedon or Drancourt as stated above teach an isolated *Tropheryma whippelii* bacterium . However, the prior art does not teach an antigen of said bacterium is used in a method of diagnosis comprising contacting the serum or any other biological fluid with bacteria or antigen on a solid support and detecting the immunological reaction.

Ken teaches a method of diagnosing whipple's disease by immunofluorescence whereas Harlow and Lane teach several immunoassays for detecting antibodies in a sample. These immunoassays are listed in Table 14.1 including the method for detecting antibody (see pages 560-561, 563). The method comprises contacting the antigen on a solid support with the test solution (i.e., serum, biological fluid etc) and detecting the antibody and antigen reaction (immunological reaction) using labeled secondary reagent.

It would have been prima facie obvious to one of ordinary skill in the art at the time invention was made to use the readily available bacteria in a method to diagnose whipple's disease because the prior art teaches how to grow bacteria and immunoassays using said bacteria as an antigen. Therefore, an artisan of ordinary skill would have been motivated to use *Tropheryma whippelii* bacterium in an immunoassay for the in vitro diagnosis of diseases associated with infections caused by *Tropheryma whippelii* because Drancourt 1999 clearly

suggests that isolation of *Tropheryma whippelii* opens the way to the production of antigen for immunological diagnosis (see page 9 of Drancourt 1999). Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to culture *Tropheryma whippelii* bacterium in an immortalized cell lines such as fibroblasts as taught by Muller et al 1999 or Drancourt 1999 in a routinely used immunoassay in a method for detecting antibodies as taught by Kent and Harlow and Lane because *Tropheryma whippelii* bacterium and the methodology for detecting the antibody are taught by these prior arts. The claimed invention is prima facie obvious over Muller or Schoedon or Drancourt in view of Kent and Harlow and Lane absent any convincing evidence to the contrary.

12. No claims are allowed.

Relevant Prior Art

13. The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

JAMA, 258; 1039-1043 and Lancet 1994, 343(8908):1288) teach strain variation and heterogeneity in diseases cause by *Tropheryma whippelii* .

Clinical and Diagnostic Laboratory Immunology, January 2002, p. 156-159, Vol. 9, No. 1 teaches monoclonal Antibodies to Immunodominant Epitope of *Tropheryma whipplei.*

Relman's (1997(J.I.D. 176: 752-754) teachings indicate *T.Whippelii is* isolated and cultured. He states that no microorganism is uncultivable when one understands the intimate growth requirements of the bacteria.

Pace et al, U.S.Patent 6,083,683 , Pace et al teach a method or in a diagnostic immunoassay kit for the diagnosis of infection (Shigella) in a biological sample (i.e., serum or any other biological fluid) comprising contacting said biological sample with a bacterium or antigen or a fragment thereof having an enhanced antigenic property wherein said bacterium is harvested from a culture and detecting an antibody present in said biological sample binding to the Shigella bacterium or fragment thereof wherein said detecting is by means of an immunoassay ,wherein said immunoassay is a radioimmunoassay, enzyme-linked immunosorbent assay (ELISA,), fluorescent immunoassay, or fluorescence polarization

immunoassay (FPIA). The immunoassay or a diagnostic immunoassay used micro titer plates (solid support) for binding bacteria or antigen, and a conjugate antibody. Thus, the art teaches immunoassays for diagnosing bacterial disease associated with bacteria using either bacterium or antigen of said bacterium.

Conclusion

14. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Mark Navarro can be reached on (571) 272-08. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER